



# NOTES

## DYSPLASTIC & PROLIFERATIVE DISORDERS

### GENERALLY, WHAT ARE THEY?

#### **PATHOLOGY & CAUSES**

- Acquired disorders caused by defective hematopoiesis

#### **CAUSES**

- Mostly idiopathic
- Gene mutations
  - JAK2 gene in most myeloproliferative disorders

#### **COMPLICATIONS**

- Can progress to serious conditions
  - Acute myelogenous leukemia (AML)

#### **SIGNS & SYMPTOMS**

- Can be asymptomatic
- When symptomatic, depends on cell line affected

#### **DIAGNOSIS**

##### **LAB RESULTS**

- Complete blood count (CBC)
  - Cell line levels
- Peripheral blood smear
  - Morphology
- Bone marrow aspiration/biopsy
  - Morphology, cellularity (normal, hypo, hyper), % of blasts
- Cytogenetic studies
  - Chromosomal abnormalities
- Molecular tests
  - Gene mutations

#### **TREATMENT**

##### **OTHER INTERVENTIONS**

- Blood transfusion
- Hematopoietic stem cell transplant

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# ESSENTIAL THROMBOCYTOSIS

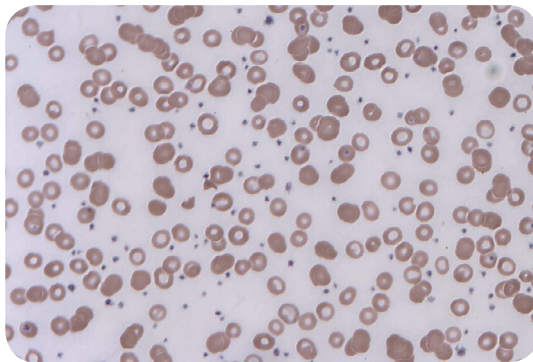
[osms.it/essential-thrombocytosis](https://osms.it/essential-thrombocytosis)

## PATHOLOGY & CAUSES

- Chronic myeloproliferative neoplasm due to **overproduction of megakaryocytes** in bone marrow
- AKA essential thrombocythemia
- ↑ platelets, abnormally shaped; ↓ platelet survival
- Thromboses; bleeding episodes may occur; other cell lines may be affected
- **JAK2 mutation** (50%), **MPL** (5–10%)/calreticulin
- “Spent phase” of myelofibrosis/AML (rarely)

## SIGNS & SYMPTOMS

- Primary symptomatic manifestations due to thrombosis → **potential ischemia in various organs, extremities** (e.g. stroke, erythromelalgia)
- Headache, dizziness, fatigue, vision loss, abdominal pain, nausea
- Less frequently, paradoxical bleeding
  - Epistaxis, bleeding gums, ecchymoses
- Splenomegaly



**Figure 45.1** A peripheral blood smear from an individual with essential thrombocytosis. There are a higher than normal number of platelets visible.

## DIAGNOSIS

### LAB RESULTS

- Platelets  $> 450 \times 10^3/\mu\text{L}$  for  $\geq$  two months; anisocytosis
- ↑ bleeding time

### Bone marrow aspiration/biopsy

- Normal cellularity

### Genetic testing

- JAK2 mutation

## OTHER DIAGNOSTICS

- History of thrombosis, bleeding, vasomotor symptoms, first trimester fetal loss

## TREATMENT

### MEDICATIONS

- Low risk for thrombosis
  - Antiplatelet drugs (aspirin, anagrelide)
- High risk for thrombosis
  - Hydroxyurea, interferon-alpha

### SURGERY

- In severe conditions
  - Plateletpheresis (removal of platelets from blood)

# LANGERHANS CELL HISTIOCYTOSIS (LCH)

[osms.it/langerhans-cell-histiocytosis](https://osms.it/langerhans-cell-histiocytosis)

## PATHOLOGY & CAUSES

- Rare, **proliferative disorder** affecting **Langerhans cells** (type of dendritic cells), myeloid progenitor cells in bone marrow
- AKA histiocytosis X
- Osteolytic bone lesions infiltrated with histiocytes; histiocytes, lymphocytes, macrophages, eosinophils infiltrate organs: skin, lymph nodes, bones, lungs, liver, spleen, central nervous system (CNS)

### Proliferating cells

- **Functionally immature**
- Immunohistochemistry
  - CD1a, S100 positive
- Abundant, foamy cytoplasm
- Folded, grooved nuclei
- **Birbeck granules**, “**tennis racket**”/rod-shaped cytoplasmic organelles

## RISK FACTORS

- Usually affects children; also present in adults
- Mutations detected; most common (55–60%) activates **BRAF** gene

## COMPLICATIONS

- CNS
  - Pituitary gland → diabetes insipidus, pons, basal ganglia; cerebellum → cognitive deficits, neuromotor dysfunction
- Liver, spleen
  - Worse prognosis; sclerosing cholangitis may require liver transplant

## SIGNS & SYMPTOMS

- **Lytic bone lesions** may be asymptomatic/cause localized pain
- Skin lesions
  - Brown to purplish **papules pustular**, **purpuric**, **petechial**, vesicular, papulonodular; eczema-like rash
- Mucous membranes
  - Gingivitis, mucosal mass/ulcers, loose teeth
- Lymphadenopathy
- Liver, spleen
  - Hepatic lesions, hepatosplenomegaly
- Lungs
  - Recurrent spontaneous pneumothorax, dyspnoea, chest pain
- CNS
  - Diabetes insipidus, neurological deficits
- Systematic symptoms
  - Fever, lethargy, weight loss

## DIAGNOSIS

### DIAGNOSTIC IMAGING

#### MRI

- CNS involvement

### LAB RESULTS

- Accumulation of inflammatory cells, Langerhans cells (large, mononuclear cells with prominent nuclear groove), few cytoplasmic vacuoles, pale eosinophilic cytoplasm

## TREATMENT

- Spontaneous regression can occur

## MEDICATIONS

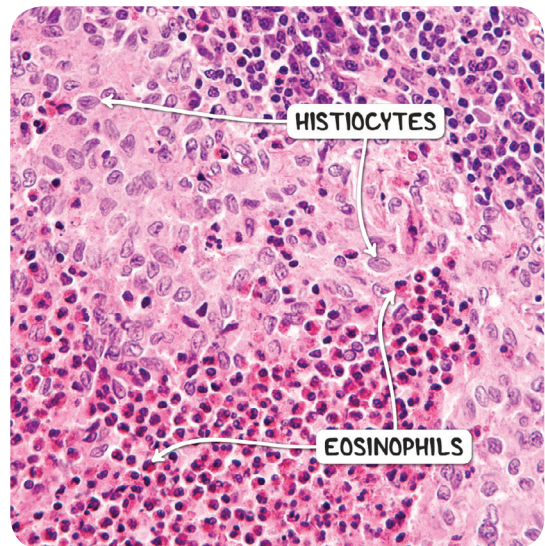
- Systemic corticosteroids
- Chemotherapeutic agents
  - Alkylating agents, antimetabolites, vinca alkaloids

## SURGERY

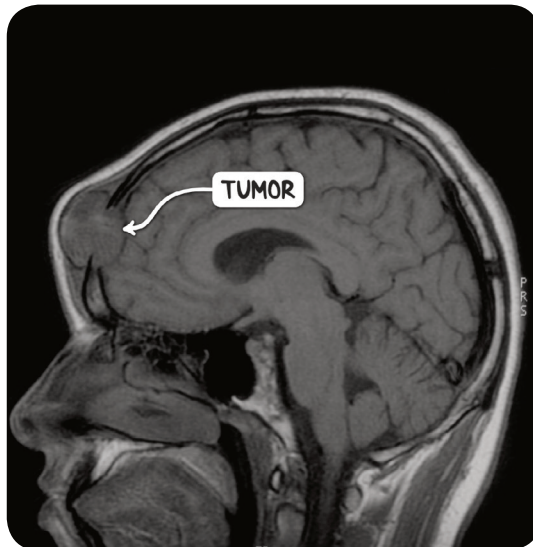
- Surgical excision

## OTHER INTERVENTIONS

- Radiation therapy



**Figure 45.2** The histological appearance of Langerhans cell histiocytosis. There are numerous clonal dendritic cells (light pink) with associated eosinophils (red).



**Figure 45.3** An MRI scan of the head in the sagittal plane demonstrating a subcutaneous soft-tissue mass, destroying the frontal bone. The diagnosis was confirmed as Langerhans histiocytosis on biopsy.

# LEUKEMOID REACTION

[osms.it/leukemoid-reaction](https://osms.it/leukemoid-reaction)

## **PATHOLOGY & CAUSES**

- **Excessive**, reactive **leukocytosis** (WBCs: 40,000–100,000/mL), resembling leukemia, with increase in neutrophil precursors, “**left shift**” (e.g. myeloblasts, promyelocytes, myelocytes) in peripheral blood
- Cytoplasmic toxic granulation, Dohle bodies, blue-gray inclusions in peripheral cytoplasm of neutrophils
- Lymphocytic reaction can occur

## **COMPLICATIONS**

- Severe/chronic infections
  - *Clostridium difficile* infection (CDI), *Mycobacterium tuberculosis*, *Bordetella pertussis*, Epstein–Barr virus (EBV)
- Sepsis
- Non-infectious inflammation
  - Burns, postoperative state, acute asthma attack, acute episodes of gout
- Severe hemolysis
- Acute hemorrhage
  - Peritoneal cavity
- Tissue necrosis
  - Hepatic necrosis, ischemic colitis
- Metastatic cancer
- Paraneoplastic syndrome
  - Lung carcinoma, renal cell carcinoma

- Drugs
  - Sulfonamides, dapsone, glucocorticosteroids, granulocyte-colony stimulating factor (G-CSF)
- Asplenia
- Metabolic
  - Diabetic ketoacidosis, preeclampsia, uremia

## **SIGNS & SYMPTOMS**

- Fatigue, weakness, high fever

## **DIAGNOSIS**

### **LAB RESULTS**

- ↑↑↑ WBCs
- Rule out blood malignancies
  - Mature neutrophil precursors, unlike immature cells in acute leukemia (blasts < 20%); toxic granulation, Döhle bodies unlike chronic myelogenous leukemia (CML)
  - Serum leukocyte alkaline phosphatase (LAP) score normal/elevated, unlike CML
  - Confirm CML by Philadelphia chromosome with *BCR/ABL* fusion gene + *FISH/PCR*
  - Bone marrow aspiration/biopsy

## **TREATMENT**

- Treatment of underlying condition

# MYELOYDYSPLASTIC SYNDROMES (MDS)

[osms.it/myelodysplastic-syndrome](https://osms.it/myelodysplastic-syndrome)

## **PATHOLOGY & CAUSES**

- Group of malignant hematopoietic stem cell disorders
- Abnormal, ineffective hematopoiesis → peripheral cytopenia

### **Dysplastic cells**

- Pseudo Pelger–Huët cells
  - Bilobed neutrophils
- Ring sideroblasts
  - Erythroblasts with granules of iron accumulated in mitochondria
- Megaloblastoid maturation
- Nuclear budding abnormalities
- Pawn ball megakaryocytes
  - Discrete nuclear lobes/multinucleation

## **CAUSES**

- Can be idiopathic/secondary to exposure
  - Toxins, genotoxic drugs, immunosuppressive agents, chemotherapy, radiation therapy (t-MDS, therapy related MDS)
- Genetic defects due to
  - Epigenetic factors, RNA splicing factors, transcription factors
  - 5q (5q-) deletion most common
- Affects elderly individuals; mean age of onset is 70 years

## **COMPLICATIONS**

- MDS = pre-leukemias, high risk of conversion to AML
- % of blasts (1–20%)
  - How close individual is to AML (> 20%)
- Progresses slowly → most succumb to bleeding, infections before AML

- Functional defects in red (RBCs), white blood cells (WBCs), platelets → anemia, infections, bleeding

## **SIGNS & SYMPTOMS**

- Asymptomatic in early stages
- Fatigue (anemia), infections (neutropenia), bleeding (thrombocytopenia)

## **DIAGNOSIS**

### **LAB RESULTS**

- Low RBCs, WBCs, platelets, normal/mildly elevated mean corpuscular volume (MCV), increased red cell distribution width (RDW)
- Low reticulocyte count, dysplastic RBCs, WBCs, normal platelets, 1–20% blasts
- Dysplastic cells, increased blasts
- Chromosomal abnormalities, gene mutations

## **TREATMENT**

### **MEDICATIONS**

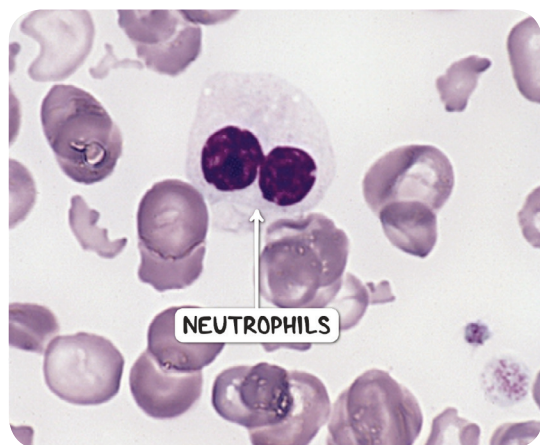
- Tumor necrosis factor (TNF) inhibitors (e.g. lenalidomide, thalidomide), DNA methylation inhibitors

### **OTHER INTERVENTIONS**

#### **Allogeneic hematopoietic stem cell transplant**

- Only curative option, for young individuals
- If transplant not an option → blood product transfusions, infection control (supportive)





**Figure 45.4** A neutrophil from a in the peripheral blood smear of an individual with myelodysplastic syndrome. The neutrophil is hypogranulated and has a hypolobated nucleus, known as a pseudo Pelger–Huët nucleus.

## POLYCYTHEMIA VERA (PCV)

[osms.it/polycythemia-vera](https://osms.it/polycythemia-vera)

### **PATHOLOGY & CAUSES**

- Chronic **myeloproliferative neoplastic** disease
- Hematopoietic stem cell disorder → erythroid, granulocytic, megakaryocytic lineages proliferate
- Increased
  - **RBCs**, independent of erythropoietin (EPO); **platelets**; basophils; eosinophils; cell turnover → **hyperuricemia**
- Polycythemia → increased blood viscosity; increased total blood volume → abnormal blood flow
- Abnormal blood flow, defective platelet function → vein thrombosis, infarcts, bleeding
- PCV may evolve to “spent phase”
  - Myelofibrosis, extramedullary hematopoiesis in liver, spleen

### **RISK FACTORS**

- Occurs in all ages; median age at diagnosis 60 years
- Genetic
  - **JAK2V617F mutation** (95% of cases)

### **COMPLICATIONS**

- Hypertension, Budd–Chiari syndrome, deep vein thrombosis, arterial thrombosis, myocardial infarction (MI), gout (high cell turnover, hyperuricemia), PCV → AML (rare)
- If untreated
  - Thrombotic, hemorrhagic complications → death within months



## SIGNS & SYMPTOMS

- Symptoms due to ↑ in RBCs → blood viscosity
  - Headache, fatigue, dizziness, dyspnea, plethora, cyanosis
- Symptoms due to ↑ in basophils → histamine release
  - Pruritus (intense itching, especially after hot shower), gastric ulcers
- Thrombosis
  - Deep vein thrombosis, MI, Budd–Chiari syndrome (portal vein thrombosis), erythromelalgia (hyperemic and inflamed extremities due to microvascular occlusion of vessels)
- Bleeding
  - Bleeding gums, epistaxis, ecchymoses, GI bleed
- Hepatosplenomegaly, splenomegaly
- Hypertension

## DIAGNOSIS

### LAB RESULTS

- Exclude secondary polycythemia (hypoxia, renal cell, hepatocellular carcinoma); ↑ EPO serum
- CBC
  - ↑ RBCs, hematocrit, hemoglobin; ↑ platelets/WBCs
- ↑ Lactate dehydrogenase
- ↓ serum EPO
- Bone marrow aspiration/biopsy confirms diagnosis
- Genetic testing
  - JAK2 mutation



**Figure 45.5** The clinical appearance of erythromelalgia; a sign of numerous diseases, including polycythemia vera.

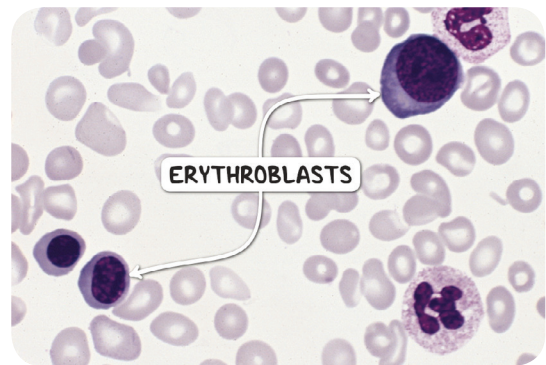
## TREATMENT

### MEDICATIONS

- Hydroxyurea
  - ↓ RBC production
- Interferon-alpha
  - ↑ RBC destruction
- Aspirin
  - ↓ risk of thrombosis

### OTHER INTERVENTIONS

- Phlebotomy
  - ↓ hematocrit, hemoglobin



**Figure 45.6** The clinical appearance of erythromelalgia; a sign of numerous diseases, including polycythemia vera.

# PRIMARY MYELOFIBROSIS (PM)

[osms.it/myelofibrosis](https://osms.it/myelofibrosis)

## **PATHOLOGY & CAUSES**

- Chronic myeloproliferative disease of hematopoietic stem cells resulting in bone marrow fibrosis
- AKA essential thrombocythemia
- **Overproduction** of **megakaryocytes** in bone marrow
- **Increased** platelets, abnormally shaped; **decreased** platelet survival
- **Thromboses**; **bleeding episodes** may occur; other cell lines may be affected
- JAK2 mutation (50%), MPL (5–10%)/calreticulin
- “Spent phase” of myelofibrosis/AML (rarely)

## **SIGNS & SYMPTOMS**

- May be asymptomatic
- When symptomatic, thrombosis, potential ischemia in various organs
  - Headache, dizziness, fatigue, numbness in extremities, erythromelalgia, vision loss, abdominal pain, nausea
- Less frequently, bleeding
  - Epistaxis, bleeding gums, bruises
- Splenomegaly

## **DIAGNOSIS**

### **LAB RESULTS**

- ↓ RBCs, platelets
- Leukoerythroblastosis, dacryocytes

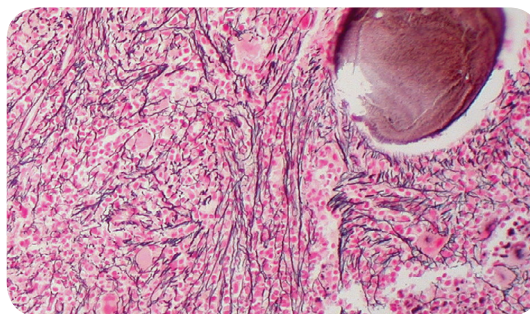
### **Bone marrow biopsy**

- Hypocellularity, fibrosis

## **OTHER INTERVENTIONS**

### **Bone marrow aspiration**

- Dry tap, no sample (accumulation of collagen fibers)



**Figure 45.7** The histological appearance of the bone marrow in an individual with myelofibrosis. The fibrosis is seen as fine silver strands upon staining with reticulin.

## **TREATMENT**

### **MEDICATIONS**

- Low risk for thrombosis
  - Antiplatelet drugs (aspirin, anagrelide)
- High risk for thrombosis
  - Hydroxyurea, interferon-alpha

### **SURGERY**

- In severe conditions
  - Plateletpheresis (removal of platelets from blood)

## DYSPLASTIC & PROLIFERATIVE DISORDERS OVERVIEW

|                                  | RBC                                                                                                                                                                | WBC                                                                                                    | PLATELETS                                                                                                                             |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| <b>POLYCYTHEMIA VERA</b>         | <p>↑↑ normocytic, normochromic RBCs</p> <p>Post-polycythemic myelofibrotic stage → leukoerythroblastic blood smear: dacrocytes, poikilocytosis, nucleated RBCs</p> | <p>↑ neutrophils</p> <p>Blasts observed as leukoerythroblastic characteristics emerge</p>              | <p>↑</p> <p>No morphological changes</p> <p>↑ megakaryocytic proliferation in bone marrow</p>                                         |
| <b>ESSENTIAL THROMBOCYTHEMIA</b> | Normal                                                                                                                                                             | Normal                                                                                                 | <p>↑↑ Anisocytosis</p> <p>↑ megakaryocytes: large, hyperlobulated (staghorn-like) nuclei</p>                                          |
| <b>MYELODYSPLASTIC SYNDROME</b>  | <p>↓</p> <p>Erythroid dysplasia: macrocytosis, multinucleation, cytoplasmic vacuoles; aniso-/poikilocytosis; ring sideroblasts</p>                                 | <p>↓</p> <p>Granulocytic dysplasia: hypogranularity; unilobed or bilobed pseudo-Pelger-Huët nuclei</p> | <p>↓</p> <p>Thrombocytic dysplasia: mega-thrombocytes; altered granulation → impaired aggregation</p> <p>Pawn ball megakaryocytes</p> |
| <b>PRIMARY MYELOFIBROSIS</b>     | <p>↓</p> <p>Leukoerythroblastosis → dacrocytes, poikilocytosis, nucleated RBCs</p>                                                                                 | <p>↑ or ↓</p> <p>Immature granulocytes; occasional pseudo-Pelger-Huët nuclei</p>                       | <p>↑ or ↓</p> <p>Megathrombocytes, altered granulation → impaired aggregation</p> <p>Megakaryocyte hyperplasia</p>                    |